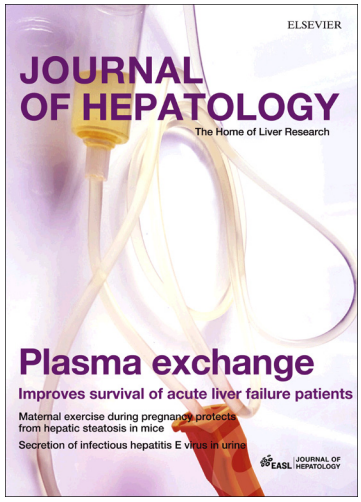

Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study

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Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study

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List of abbreviations: HCC, hepatocellular carcinoma; GIDEON, Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib; AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor node metastasis; CI, confidence interval; INR, international normalized ratio

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HealthCare Pharmaceuticals and Onyx Pharmaceuticals, an Amgen subsidiary. Professors Lencioni and Bronowicki have received honoraria for advisory arrangements from Bayer HealthCare Pharmaceuticals. Professor Papandreou has received research grant support from Bayer HealthCare Pharmaceuticals. Dr Nakajima, Mr Lehr, and Ms Heldner are employees of Bayer HealthCare Pharmaceuticals. Dr Nakajima has stock ownership with Bayer HealthCare Pharmaceuticals. Drs Kudo, Chen, Dagher, Ladrón de Guevara, Sanyal, Takayama, Yoon, and Ye have no relevant disclosures to report.

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Abstract

Background & Aims: GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) is a prospective, observational registry study evaluating the safety of sorafenib and treatment practices in hepatocellular carcinoma patients. This large global database allowed for assessment of the use and tolerability of sorafenib in patients with liver dysfunction.

Methods: Baseline characteristics and medical/treatment history were collected in patients for whom a decision to treat with sorafenib had been made. Adverse-event, dosing, and outcomes data were collected during follow-up.

Results: In the overall safety population (n = 3202), 1968 patients (61%) had Child-Pugh A status and 666 (21%) had Child-Pugh B. The majority of Child-Pugh A (72%) and Child-Pugh B (70%) patients received an initial sorafenib dose of 800 mg, consistent with the label, and dose-reduction rates were 40% and 29%, respectively. The type and incidence of adverse events were generally consistent across Child-Pugh subgroups. The incidence of drug-related adverse events leading to discontinuation was similar between Child-Pugh A and Child-Pugh B patients (17% and 21%). In the intent-to-treat population (n = 3213), median overall survival (months [95% confidence interval]) was longer in Child-Pugh A patients (13.6 [12.8–14.7]) compared with Child-Pugh B patients (5.2 [4.6–6.3]).

Conclusions: In clinical practice, the safety profile of sorafenib appeared to be consistent across Child-Pugh A and Child-Pugh B patients. Findings suggest sorafenib may be safely used in some Child-Pugh B patients and indicate the importance of careful patient evaluation when making treatment decisions.

Abstract word count: 248

Keywords: hepatocellular carcinoma; HCC; sorafenib; Nexavar; Child-Pugh; GIDEON

Introduction

Liver cancer is the second leading cause of cancer-related death worldwide [1]. The majority of primary liver cancer presents as hepatocellular carcinoma (HCC), the incidence of which is rising in many parts of the world [2]. The vast majority of HCC cases occur in the setting of liver cirrhosis, usually because of chronic hepatitis C or hepatitis B viral infections, alcohol consumption, non-alcoholic steatohepatitis, or diabetes [3]. The degree of underlying liver disease, as well as the tumor stage and patients' general condition, must therefore be considered when making treatment decisions for HCC. Most HCC patients have advanced disease at diagnosis, or present with recurrent disease following potentially curative treatments [4]. Therefore, systemic therapy with the oral multikinase inhibitor sorafenib (Nexavar®; Bayer Pharma AG, Berlin, Germany) plays a key role in the management of HCC [5].

Sorafenib was approved for the treatment of unresectable HCC after two Phase III trials (SHARP and Asia-Pacific) demonstrated significant improvements in overall survival [6,7]. Sorafenib is the first-line therapy in patients with advanced HCC [8]; however, pivotal trials, like most clinical trials in HCC, included only patients with Child-Pugh A status in order to avoid confounding results because of the presence of liver dysfunction [7]. Hence, data on the use and safety of sorafenib in HCC patients with Child-Pugh B status are currently limited [9].

The Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib (GIDEON) trial was a prospective, observational registry study undertaken to evaluate the safety and use of sorafenib in HCC patients under real-life practice conditions, and, in particular, to gather more comprehensive data on the use of sorafenib in patients with Child-Pugh B liver function. GIDEON is one of the largest efforts ever undertaken in

patients with HCC, and allows for a broad evaluation of disease characteristics, treatment practices, and safety across patient subgroups.

Here we present data from the final analysis of GIDEON, including how liver function was assessed, patient and disease characteristics, treatment practices, adverse events, and outcomes, in HCC patients with advanced liver dysfunction treated with sorafenib.

Methods

Study design

GIDEON included patients for whom a decision to treat with sorafenib was made by their physician in clinical practice. All decisions concerning patient assessment, including liver function, sorafenib dose, and duration of treatment, were solely at the discretion of the attending physician and not mandated by the study protocol.

Eligible patients were those diagnosed histologically, cytologically, or radiographically with HCC, with a life expectancy of more than 8 weeks. Exclusion criteria were based on the prescribing information for sorafenib. Full details of the study design, including further inclusion criteria, have been previously published [10]. GIDEON enrollment began in January 2009 and the last patient follow-up occurred in April 2012. Final analysis was undertaken at 12-month follow-up following the enrollment of 3000 sorafenib-treated patients.

Data collection and analyses

All patients provided informed and signed consent. GIDEON was conducted within an approved indication in accordance with the guidelines of the European Medicines Agency and the US Food and Drug Administration relating to non-interventional and post-

authorization safety studies and Good Clinical Practice, as outlined in Directive 2001/20/EC [11]. Documented approval from appropriate ethics committees and institutional review boards was obtained in accordance with local laws, regulations, and organizations.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients who received at least one dose of sorafenib and underwent at least one follow-up assessment were evaluable for safety, while the intent-to-treat population comprised any patient who received one or more doses of sorafenib. For evaluation of liver dysfunction, Child-Pugh score was calculated based on the composite score of five variables: bilirubin, albumin, ascites, encephalopathy, and international normalized ratio [12]. All data were collected by the treating physician via case report forms.

Target enrollment was based on an overall sample of 3000 patients, the number determined sufficient for comprehensive evaluation of safety for the overall population, as well as specified subgroups [10]. All data were collected and monitored centrally and summarized with descriptive statistics.

Results

Patient disposition

A total of 3371 patients were enrolled from 39 countries across five regions (USA, Europe, Japan, Latin America, and Asia-Pacific). The safety population comprised 3202 patients and the intent-to-treat population comprised 3213 patients. Within the safety population, 2708 patients had known Child-Pugh status at the start of sorafenib therapy; of these, 73% (n = 1968) had Child-Pugh A, 25% (n = 666) had Child-Pugh B, and 3% (n = 74) had Child-Pugh C (**Fig. 1**). In the intent-to-treat population, 2717 patients had known Child-Pugh status

(n = 1975 [73%] Child-Pugh A, n = 669 [25%] Child-Pugh B, and n = 73 [3%] Child-Pugh C).

Overall, in the safety population, 15% (n = 494) of patients did not have all of the required information in order to be evaluable for Child-Pugh status. The most commonly absent assessments were international normalized ratio/prothrombin time and albumin. Notably, the USA had the highest frequency of missing values for all of the assessments, with 30% of patients non-evaluable for Child-Pugh score (**Supplementary Table 1**).

Baseline patient demographics and disease characteristics

The median age was 64 years for Child-Pugh A patients and 61 years for Child-Pugh B patients, and the majority of patients in all Child-Pugh subgroups were male (**Table 1**). The proportion of patients with Child-Pugh A status was highest in Japan (75%) and lowest in the USA (46%). Barcelona Clinic Liver Cancer (BCLC) and tumor node metastasis stages were similar between Child-Pugh A and Child-Pugh B patients (**Table 1**).

Sorafenib administration by Child-Pugh status

Overall, sorafenib dosing was similar irrespective of Child-Pugh score. The majority of Child-Pugh A and Child-Pugh B patients received the recommended initial dose of 800 mg (72% and 70%, respectively), while this was slightly lower for patients with Child-Pugh C status (62%). The median daily dose was also comparable between Child-Pugh A and Child-Pugh B patients (677 mg and 742 mg, respectively). A slightly higher proportion of Child-Pugh A patients (40%) had a dose reduction at any time during the study period compared with Child-Pugh B patients (29%) (**Table 2**).

The initial sorafenib dose and the proportion of patients with a dose reduction or increase were also comparable across patients with baseline bilirubin levels of less than 2.0 mg/dL, 2.0–3.0 mg/dL, or greater than 3.0 mg/dL (**Supplementary Table 2**).

The median duration of treatment was longer in Child-Pugh A patients (17.6 weeks) compared with Child-Pugh B patients (9.9 weeks) and Child-Pugh C patients (5.6 weeks) (**Table 2**). Similarly, Child-Pugh B7 patients tended to have a longer duration of therapy (11.1 weeks) than Child-Pugh B8 patients (9.3 weeks) and Child-Pugh B9 patients (7.6 weeks).

The proportion of patients discontinuing within 8 weeks was lower for Child-Pugh A patients (26%) compared with Child-Pugh B patients (42%), with 38%, 44%, and 49% of B7, B8, and B9 patients discontinuing within 8 weeks, respectively. The proportion of Child-Pugh A and Child-Pugh B patients remaining on sorafenib for more than 28 weeks was 33% and 20%, respectively (**Table 2**). Those patients who continued sorafenib beyond 28 weeks tended to have higher baseline albumin, lower baseline bilirubin, and no ascites (**Table 3**).

Sorafenib safety assessments

The overall incidence of AEs and drug-related AEs was comparable between Child-Pugh A and Child-Pugh B patients, as was the incidence of grade 3 or 4 AEs; however, serious AEs were more common in Child-Pugh B patients. The incidence of serious AEs was higher in Child-Pugh B patients with a score of 8 or 9 compared with Child-Pugh B patients with a score of 7 (**Table 4**). The safety profile according to BCLC–Child-Pugh cross-classification was generally consistent with the data across Child-Pugh subgroups. For Child-Pugh A patients, a higher proportion of deaths was seen for those with BCLC C or D status compared with those with BCLC A or B status (**Supplementary Table 3**).

The most commonly reported AEs across all Child-Pugh subgroups were diarrhea, hand-foot skin reaction, and fatigue. The incidence of individual AEs and drug-related AEs was similar in Child-Pugh A and Child-Pugh B patients, with the exception of hand-foot skin reaction, which was more common in Child-Pugh A patients (**Table 5**).

The majority of AEs grade 3 or higher occurred during the first 4 weeks of treatment in both Child-Pugh A and Child-Pugh B patients (**Fig. 2**). The rate of the most common AEs, calculated as event per patient-year, was also comparable in these groups (**Supplementary Table 4**).

In total, AEs leading to permanent discontinuation were more common in Child-Pugh B (40%) and C (43%) patients than in Child-Pugh A patients (29%), although the incidences of drug-related AEs leading to discontinuation were similar (21%, 15%, and 17%, respectively). The incidences of individual AEs and drug-related AEs leading to permanent discontinuation were also similar in Child-Pugh A and Child-Pugh B subgroups. The types of AEs leading to sorafenib discontinuation were various, with no AE leading to discontinuation in more than 5% of patients overall (**Supplementary Table 5**). In Child-Pugh B patients, AEs leading to discontinuation occurred most commonly during the first 4 weeks of treatment (**Supplementary Table 6**).

The overall incidence of AEs leading to permanent discontinuation was similar in patients with baseline bilirubin less than 2.0 mg/dL (85%) and 2.0–3.0 mg/dL (84%), although this was higher in patients with bilirubin greater than 3.0 mg/dL (95%). The overall incidence of drug-related AEs and the incidence of drug-related AEs leading to permanent discontinuation were comparable irrespective of bilirubin level (**Supplementary Table 7**).

Survival

In the intent-to-treat population, median overall survival was longer in Child-Pugh A patients (13.6 months) than in Child-Pugh B patients (5.2 months) and Child-Pugh C patients (2.6 months), as anticipated (**Fig. 3A**). Median overall survival in Child-Pugh B7 patients (6.2 months) was considerably shorter than in Child-Pugh A patients, but was longer than in Child-Pugh B8 patients (4.8 months) and Child-Pugh B9 patients (3.7 months) (**Fig. 3B**). Median overall survival according to BCLC by Child-Pugh cross-classification followed a similar trend, as patients with Child-Pugh A and BCLC stage B had longer overall survival compared with patients with Child-Pugh B and BCLC stage B (19.5 months vs 10.0 months), and patients with Child-Pugh A and BCLC stage C had longer overall survival compared with patients with Child-Pugh B and BCLC stage C (11.2 months vs 3.8 months) (**Supplementary Fig. 1**).

Of the individual components of Child-Pugh score, albumin level, ascites, and bilirubin level all appeared to be prognostically valuable for overall survival, as did encephalopathy to a lesser degree (**Supplementary Fig. 2**). However, it should be noted that ascites could be evaluated clinically or radiologically by the treating physician, and no allowance for possible treatment with diuretics was made when assessing ascites. In addition, the patient numbers in the moderate and severe groups for encephalopathy were extremely low, meaning these data should be interpreted with caution. International normalized ratio did not appear to be predictive of survival (**Supplementary Fig. 2**). These findings are also supported by a univariate Cox regression analysis in which the hazard ratio (95% confidence interval) for survival was 1.708 (1.573–1.855) for bilirubin and 1.755 (1.629–1.892) for albumin (**Supplementary Table 8**).

Discussion

The final analysis of the GIDEON registry provides insight into patients with HCC treated with sorafenib in real-life practice, thereby allowing evaluation across clinically relevant subgroups. In particular, the safety of sorafenib in HCC patients with poorer liver function remains an unanswered question, as pivotal Phase III trials of sorafenib excluded Child-Pugh B patients.

In the GIDEON registry, the safety profile of sorafenib observed was similar between Child-Pugh A and Child-Pugh B patients, and was in line with the known safety profile of sorafenib [6,7]. The rate of the most common AEs was also broadly comparable between Child-Pugh groups, suggesting that the similar incidences observed were not due to the shorter duration of treatment in Child-Pugh B patients. These findings in this large international registry study support those from several smaller studies [13–17], suggesting that sorafenib tolerability is not remarkably different between Child-Pugh A and Child-Pugh B patients.

The greatest number of AEs occurred during the first 4 weeks of treatment irrespective of Child-Pugh score, which likely explains the high rate of discontinuation seen in this period across Child-Pugh subgroups. Notably, in the SHARP Phase III trial, discontinuation due to AEs was comparable between the placebo and sorafenib groups (30% and 29%) [6], indicating that discontinuation due to AEs may be related to the underlying disease in some cases. A large proportion of patients were able to continue sorafenib treatment beyond 28 weeks, including 21% of Child-Pugh B patients, suggesting that patients who are able to continue treatment beyond the initial period are able to subsequently continue for long periods, and highlighting the importance of AE management in the first weeks of treatment [18]. Discontinuation due to AEs was higher in Child-Pugh B patients compared with Child-Pugh A, while discontinuation due to drug-related AEs was comparable. Similarly,

discontinuation due to AEs, but not drug-related AEs, was higher in patients with baseline bilirubin greater than 3.0 mg/dL than in those with lower bilirubin levels. This suggests that in some cases physicians may be more likely to discontinue treatment in patients with advanced cirrhosis, and indicates that patients with a stable degree of liver dysfunction are able to continue sorafenib.

Previous studies have reported differences in AE incidence between Child-Pugh subgroups; however, it could not be determined if such differences were drug-related or due to disease progression [19]. A further report found that sorafenib was associated with dose-limiting toxicity in HCC patients with baseline bilirubin less than 1.5 times the upper limit of normal, with the main dose-limiting toxicity reported being elevated bilirubin [20]. However, in GIDEON, the safety profile of sorafenib was similar in patients with bilirubin levels less than 2.0 mg/dL and 2.0–3.0 mg/dL.

The data suggest that physicians' approaches to sorafenib dosing in clinical practice do not differ based on liver dysfunction, and are in accordance with the approved prescribing information in most cases. The initial sorafenib dose, median daily dose, and proportion of patients receiving a dose increase or reduction were broadly similar irrespective of the degree of liver dysfunction.

Together, the combined findings from GIDEON therefore suggest that dose modification is not required based solely on the degree of baseline liver dysfunction. This is supported by pharmacokinetic studies which have demonstrated there is no difference in the pharmacokinetic profile of sorafenib in Child-Pugh A and Child-Pugh B patients [14,19,21,22] and is reflected in the prescribing information [23]. However, because of the heterogeneous nature of patients categorized as Child-Pugh B, detailed assessment is required when deciding the most appropriate treatment option.

In line with previous studies, median overall survival was shorter in Child-Pugh B patients compared with Child-Pugh A patients [14,24]. The poorer outcomes observed in Child-Pugh B patients were as expected and likely relate to the natural progression of cirrhosis in these patients with more advanced disease [19,25]. However, because of the observational nature of the GIDEON study and lack of a control, the efficacy of sorafenib in Child-Pugh B patients cannot be assessed. Previous reports suggest that while Child-Pugh B patients have poorer outcomes compared with Child-Pugh A, sorafenib may offer clinical benefit in carefully selected Child-Pugh B patients [24,26,27].

Median overall survival and univariate Cox regression analysis highlighted that baseline bilirubin and albumin levels strongly influenced prognosis. Interestingly, higher albumin and lower bilirubin levels appeared to be associated with longer sorafenib treatment. These data therefore suggest that albumin and bilirubin levels may be of particular importance when considering the use of sorafenib therapy in patients with liver dysfunction. This is supported by the recent description of the Albumin-Bilirubin grade system, which stratifies HCC patients into three risk categories based on serum bilirubin and albumin levels only, and has shown to predict survival equally as well as the Child-Pugh system [28].

As GIDEON is an observational registry study, it is inherently limited by the lack of a randomized, controlled population and the potential for selection bias. The descriptive statistics employed do not allow for conclusive analysis of outcomes. In addition, no measure of compliance was collected. That said, real-life observational studies such as GIDEON provide an opportunity to assess treatment patterns in clinical practice, and allow for the assessment of a wider patient population than in randomized clinical trials.

It has been reported that certain AEs, such as skin toxicity [29–31] or diarrhea [32], may act as biomarkers for sorafenib efficacy. In GIDEON, no obvious correlation between any AE

and response was seen; however, because of the observational nature of the study, formal analysis of outcomes based on post-baseline factors was not considered appropriate. Further robust data are required to validate if any AE is a reliable pharmacodynamic biomarker for sorafenib efficacy.

Interestingly, a large number of patients enrolled did not have all of the required elements for Child-Pugh classification, particularly in the USA. International normalized ratio and albumin were the most common omissions, suggesting that many physicians may not routinely score Child-Pugh in clinical practice (even when data are being collected by a sponsor) or may assess liver disease based on other parameters.

In summary, these findings from the final analysis of GIDEON confirm that sorafenib is used clinically across a broad spectrum of HCC patients, including those with liver dysfunction. In this cohort, the safety profile of sorafenib was generally consistent in Child-Pugh A and Child-Pugh B patients. Despite a similar safety profile, a higher rate of treatment discontinuation was observed in patients with Child-Pugh B status, who have a poorer general condition. The data show that Child-Pugh B patients are heterogeneous, and highlight that certain factors may be especially important in the assessment of patients with liver dysfunction, emphasizing the need for careful assessment when making treatment decisions in these patients. Together, the data indicate the use of the recommended sorafenib dose with subsequent monitoring as an appropriate treatment option in HCC patients with more advanced liver dysfunction.

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Author contributions

JAM, RL, MK, S-LY, and APV are members of the Global Steering and Publication Committee for the GIDEON study and were involved in modification of the GIDEON protocol, and in data review and interpretation. JAM, RL, MK, S-LY, APV, J-PB, X-PC, LD, JF, JFG, LL de G, CP, AJS, TT, and SKY were all responsible for the provision of patients and data acquisition. KN is the sponsor study physician and contributed to data analysis and interpretation. RLehr is the study statistician and contributed to statistical analysis. SH was responsible for the study supervision. All authors provided critical review of the manuscript for intellectual content, and approved the final version for publication.

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Table 1. Baseline patient and disease characteristics by Child-Pugh score.

	Child-Pugh score[a,b]					
	A (<7)	**B7**	**B8**	**B9**	**B (7–9)[c]**	**C (>9)**
Patients, n (% of total)	1968 (61)	359 (11)	182 (6)	122 (4)	666 (21)	74 (2)
Median age, years (range)	64 (15–94)	61 (19–87)	62 (32–84)	56 (31–79)	61(19–87)	58 (29–82)
Gender, n (%)						
Male	1618 (82)	302 (84)	143 (79)	94 (77)	542 (81)	61 (82)
Female	350 (18)	57 (16)	39 (21)	28 (23)	124 (19)	13 (18)
ECOG PS, n (%)[a,d]						
0 or 1	1741 (89)	278 (77)	124 (68)	77 (63)	481 (72)	44 (59)
≥2	142 (7)	58 (16)	47 (26)	36 (30)	142 (21)	27 (37)
BCLC stage, n (%)[a,e]						
A	158 (8)	22 (6)	10 (6)	5 (4)	37 (6)	0
B	435 (22)	74 (21)	36 (20)	26 (21)	136 (20)	0
C	1124 (57)	199 (55)	106 (58)	66 (54)	373 (56)	1 (1)
D	60 (3)	15 (4)	7 (4)	8 (7)	30 (5)	66 (89)
TNM status, n (%)[a,f,g]						
I	104 (5)	10 (3)	9 (5)	9 (7)	28 (4)	5 (7)
II	287 (15)	33 (9)	18 (10)	10 (8)	61 (9)	10 (14)
III	701 (36)	158 (44)	80 (44)	46 (38)	286 (43)	25 (34)
IV	717 (36)	119 (33)	55 (30)	41 (34)	215 (32)	22 (30)
Bilirubin (mg/dL)[h]						
<2.0	1906 (97)	262 (73)	76 (42)	28 (23)	367 (55)	6 (8)
2.0–3.0	61 (3)	87 (24)	66 (36)	43 (35)	197 (30)	21 (28)
>3.0	1 (<0.1)	10 (3)	40 (22)	51 (42)	102 (15)	47 (64)
Albumin (g/L)[i]						
>35.0	1480 (75)	68 (19)	16 (9)	2 (2)	86 (13)	2 (3)
28.0–35.0	482 (25)	224 (62)	131 (72)	63 (52)	420 (63)	19 (26)
<28.0	1 (<0.1)	67 (19)	35 (19)	57 (47)	160 (24)	53 (72)
International normalized ratio (seconds)[i]						
<1.7	1942 (99)	324 (90)	158 (87)	96 (79)	581 (87)	41 (55)

1.7–2.3	24 (1)	23 (6)	16 (9)	24 (20)	63 (9)	17 (23)
>2.3	0	12 (3)	8 (4)	2 (2)	22 (3)	16 (22)
Encephalopathy[k]						
Absent	1960 (100)	347 (97)	177 (97)	112 (92)	637 (96)	52 (70)
Moderate (stage I or II)	7 (<1)	12 (3)	5 (3)	9 (7)	26 (4)	19 (26)
Severe (stage III or IV)	0	0	0	1 (1)	1 (<1)	2 (3)
Ascites[l]						
Absent	1830 (93)	190 (53)	70 (39)	34 (28)	294 (44)	8 (11)
Slight	138 (7)	144 (40)	62 (34)	49 (40)	256 (38)	25 (34)
Moderate	0	25 (7)	50 (28)	39 (32)	116 (17)	41 (55)
HCC features, n (%)[a]						
Extrahepatic spread	813 (41)	138 (38)	59 (32)	44 (36)	242 (36)	18 (24)
Vascular invasion	432 (22)	100 (28)	61 (34)	29 (24)	191 (29)	22 (30)
Etiology of liver disease, n (%)[m]						
Hepatitis B	763 (39)	122 (34)	53 (29)	41 (34)	218 (33)	19 (26)
Hepatitis C	628 (32)	134 (37)	72 (40)	43 (35)	251 (38)	34 (46)
Alcohol use[n]	435 (22)	121 (34)	67 (37)	49 (40)	237 (36)	28 (38)

[a]Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); [b]Child-Pugh status missing for one patient; [c]Three patients recorded as having Child-Pugh B but specific score not recorded; [d]Data missing for 194 patients; [e]Data missing for four patients; 501 patients non-evaluable; [f]Data missing for four patients; 391 patients non-evaluable; [g]TNM assessment based on radiological evaluation; [h]Data missing for 128 patients; [i]Data missing for 223 patients; [j]Data missing for 370 patients; [k]Data missing for 132 patients; [l]Data missing for 113 patients; ascites assessed clinically or radiologically; [m]Based on patients with recorded etiology (n = 3195); patients may have more than one etiology; [n]Alcohol use was defined as any patient for whom the treating physician recorded alcohol as a potential cause of liver dysfunction.

ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor node metastasis.

Table 2. Sorafenib administration across Child-Pugh subgroups.

	Child-Pugh score[a,b]					
	A (<7) (n = 1968)	**B7 (n = 359)**	**B8 (n = 182)**	**B9 (n = 122)**	**B (7–9)[c] (n = 666)**	**C (>9) (n = 74)**
Initial dose, n (%)						
800 mg	1415 (72)	253 (70)	129 (71)	79 (65)	464 (70)	46 (62)
400 mg	482 (25)	91 (25)	47 (26)	35 (29)	173 (26)	21 (28)
Median daily dose[d], mg	677.0	725.0	756.5	753.0	741.5	603.5
Dose reduction, n (%)	784 (40)	110 (31)	54 (30)	30 (25)	194 (29)	19 (26)
Dose increase, n (%)	413 (21)	52 (14)	25 (14)	23 (19)	100 (15)	8 (11)
Median time from diagnosis to initiation of sorafenib, months	4.9	2.8	2.5	2.4	2.5	1.3
Median treatment duration[e], weeks	17.6	11.1	9.3	7.6	9.9	5.6
Duration of treatment[f]						
≤8 weeks	510 (26)	137 (38)	80 (44)	60 (49)	279 (42)	41 (55)
>8–28 weeks	781 (40)	125 (35)	58 (32)	38 (31)	222 (33)	22 (30)
>28 weeks	651 (33)	78 (22)	41 (23)	17 (14)	136 (20)	8 (11)

[a]Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); [b]Child-Pugh status missing for one patient; [c]Three patients recorded as having Child-Pugh B but specific score not recorded; [d]Based on patients with available data (n = 2857); [e]Based on patients with available data (n = 3130); [f]Data missing for 72 patients.

Table 3. Disease characteristics by treatment duration beyond 28 weeks.

n (%)	≤28 weeks (n = 2259)	>28 weeks (n = 943)
Bilirubin (mg/dL)		
<2.0	1774 (79)	810 (86)
2.0–3.0	251 (11)	62 (7)
>3.0	152 (7)	25 (3)
Albumin (g/L)		
>35.0	1127 (50)	599 (64)
28.0–35.0	781 (35)	227 (24)
<28.0	203 (9)	42 (5)
International normalized ratio (seconds)		
<1.7	1891 (84)	791 (84)
1.7–2.3	74 (3)	34 (4)
>2.3	32 (1)	10 (1)
Encephalopathy		
Absent	2114 (93)	891 (94)
Moderate	42 (2)	20 (2)
Severe	3 (<1)	0
Ascites		
Absent	1641 (73)	786 (83)
Slight	379 (17)	100 (11)
Moderate	162 (7)	21 (2)

Table 4. Overall safety profile of sorafenib by Child-Pugh score.

n (%)	Child-Pugh score[a,b]					
	A (<7) (n = 1968)	B7 (n = 359)	B8 (n = 182)	B9 (n = 122)	B (7–9)[c] (n = 666)	C (>9) (n = 74)
AEs (all grades)	1653 (84)	313 (87)	166 (91)	109 (89)	590 (89)	68 (92)
Drug-related AEs (all grades)	1349 (69)	240 (67)	114 (63)	74 (61)	429 (64)	29 (39)
Serious AEs[d]	708 (36)	192 (54)	126 (69)	82 (67)	402 (60)	52 (70)
Drug-related serious AEs	174 (9)	48 (13)	28 (15)	18 (15)	94 (14)	2 (3)
All grade 3 or 4 AEs	638 (33)	109 (30)	57 (31)	44 (36)	210 (32)	13 (18)
Drug-related grade 3 or 4 AEs	503 (26)	79 (22)	41 (23)	26 (21)	146 (22)	8 (11)
Deaths[e]	349 (18)	113 (31)	78 (43)	46 (38)	239 (36)	38 (51)

[a]Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); [b]Child-Pugh status missing for one patient; [c]Three patients recorded as having Child-Pugh B but specific score not recorded; [d]Any AE occurring at any dose that results in any of the following outcomes: death; life-threatening; hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; medically important event; [e]Treatment-emergent deaths occurring up to 30 days after last sorafenib dose.

Table 5. Incidence of adverse events and drug-related adverse events occurring in ≥10% of patients by Child-Pugh score.

n (%)	Child-Pugh score[a,b]											
	A (<7) (n = 1968)		B7 (n = 359)		B8 (n = 182)		B9 (n = 122)		B (7–9)[c] (n = 666)		C (>9) (n = 74)	
	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE	AE	Drug-related AE
Diarrhea	616 (31)	556 (28)	112 (31)	98 (27)	52 (29)	48 (26)	31 (25)	23 (19)	196 (29)	170 (26)	13 (18)	8 (11)
Hand-foot skin reaction	636 (32)	626 (32)	70 (20)	70 (20)	29 (16)	29 (16)	14 (11)	14 (11)	116 (17)	113 (17)	4 (5)	4 (5)
Fatigue	440 (22)	311 (16)	98 (27)	56 (16)	43 (24)	22 (12)	30 (25)	17 (14)	171 (26)	95 (14)	15 (20)	10 (14)
Anorexia	285 (15)	209 (11)	57 (16)	30 (8)	29 (16)	11 (6)	14 (11)	8 (7)	100 (15)	49 (7)	10 (14)	5 (7)
Abdomen pain	224 (11)	62 (3)	63 (18)	26 (7)	31 (17)	8 (4)	23 (19)	6 (5)	118 (18)	24 (4)	13 (18)	4 (5)
Liver dysfunction[d]	203 (10)	36 (2)	46 (13)	10 (3)	43 (24)	7 (4)	30 (25)	2 (2)	120 (18)	19 (3)	16 (22)	0
Rash/desquamation	258 (13)	238 (12)	41 (11)	35 (10)	17 (9)	15 (8)	8 (7)	7 (6)	66 (10)	57 (9)	4 (5)	3 (4)
Nausea	167 (8)	106 (5)	42 (12)	28 (8)	19 (10)	8 (4)	9 (7)	5 (4)	70 (11)	41 (6)	9 (12)	7 (9)
Hypertension	243 (12)	215 (11)	21 (6)	18 (5)	7 (4)	7 (4)	3 (2)	3 (2)	31 (5)	28 (4)	0	0

[a]Recorded at study entry (which is defined as start of therapy and is indicated by the initial visit); [b]Child-Pugh status missing for one patient; [c]Three patients recorded as having Child-Pugh B but specific score not recorded; [d]Liver dysfunction as an adverse event was based on physicians' selection on case report forms.

Figure legends

Fig. 1. Patient disposition.

ITT, intent-to-treat.

Fig. 2. Onset time of adverse events grade ≥3 in Child-Pugh A and Child-Pugh B patients.

Fig. 3. Median overall survival across Child-Pugh subgroups.

Kaplan-Meier analysis of median overall survival: (A) Child-Pugh subgroups; (B) Child-Pugh B subgroups. CI, confidence interval.

Figure 1

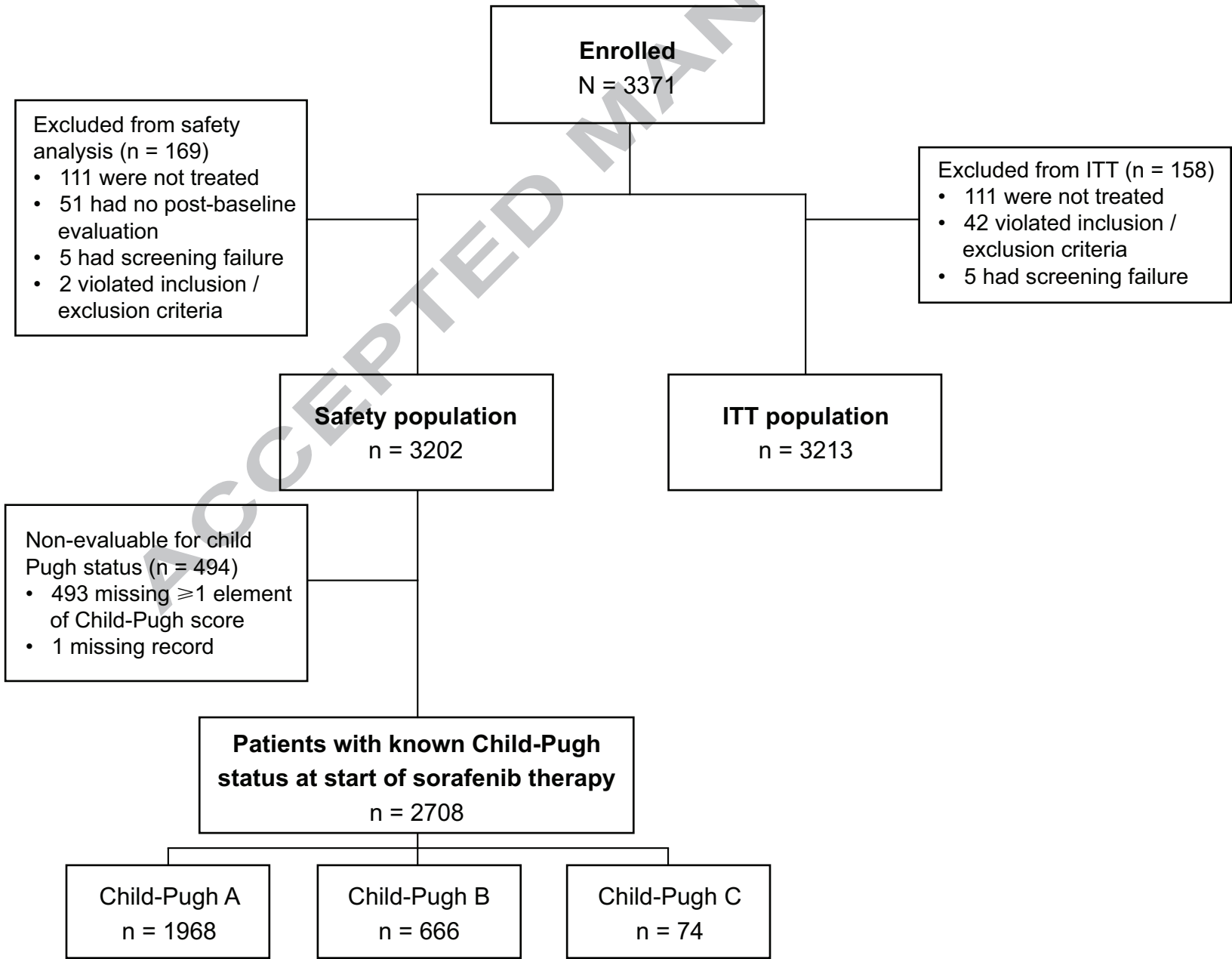
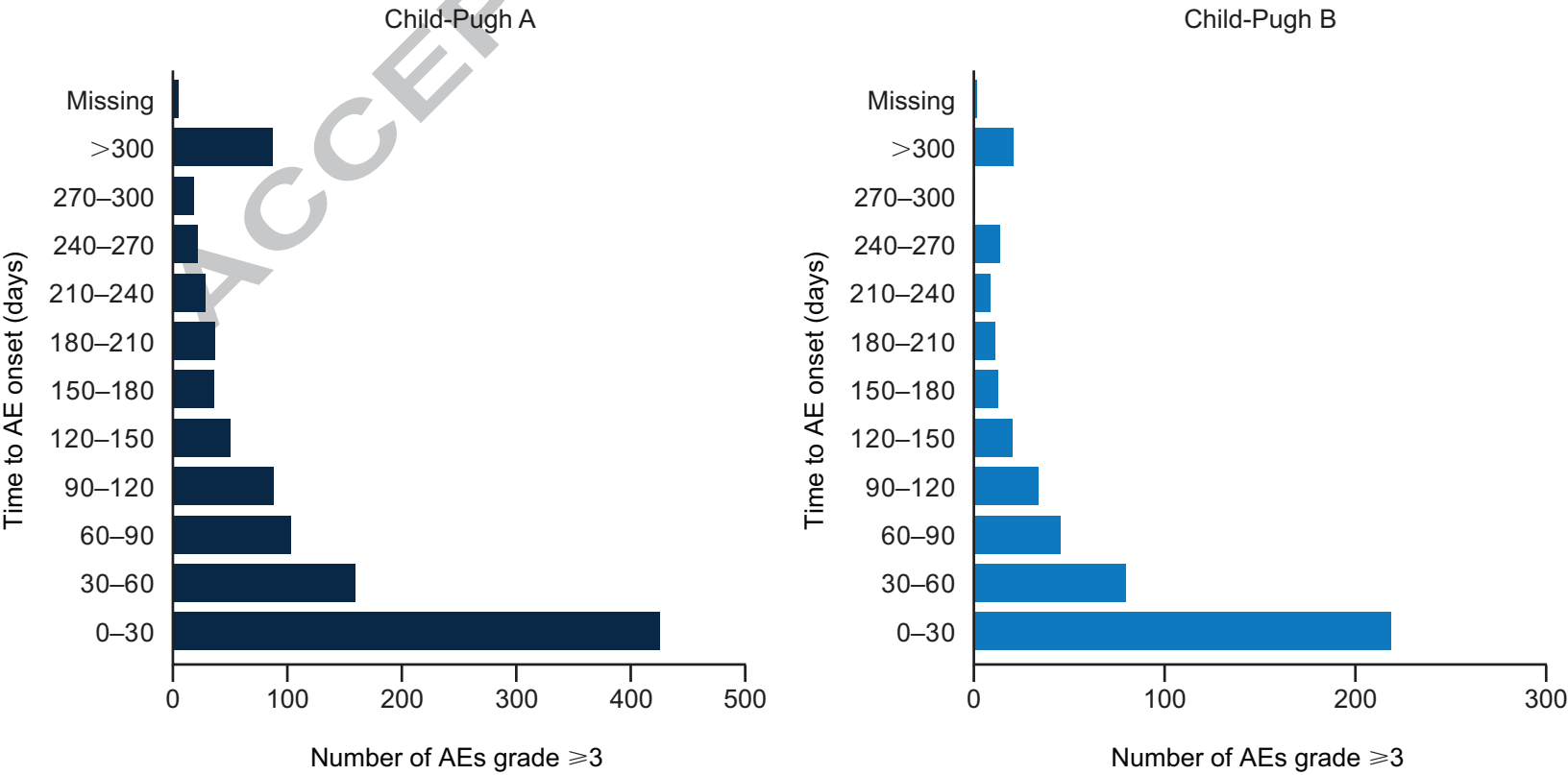
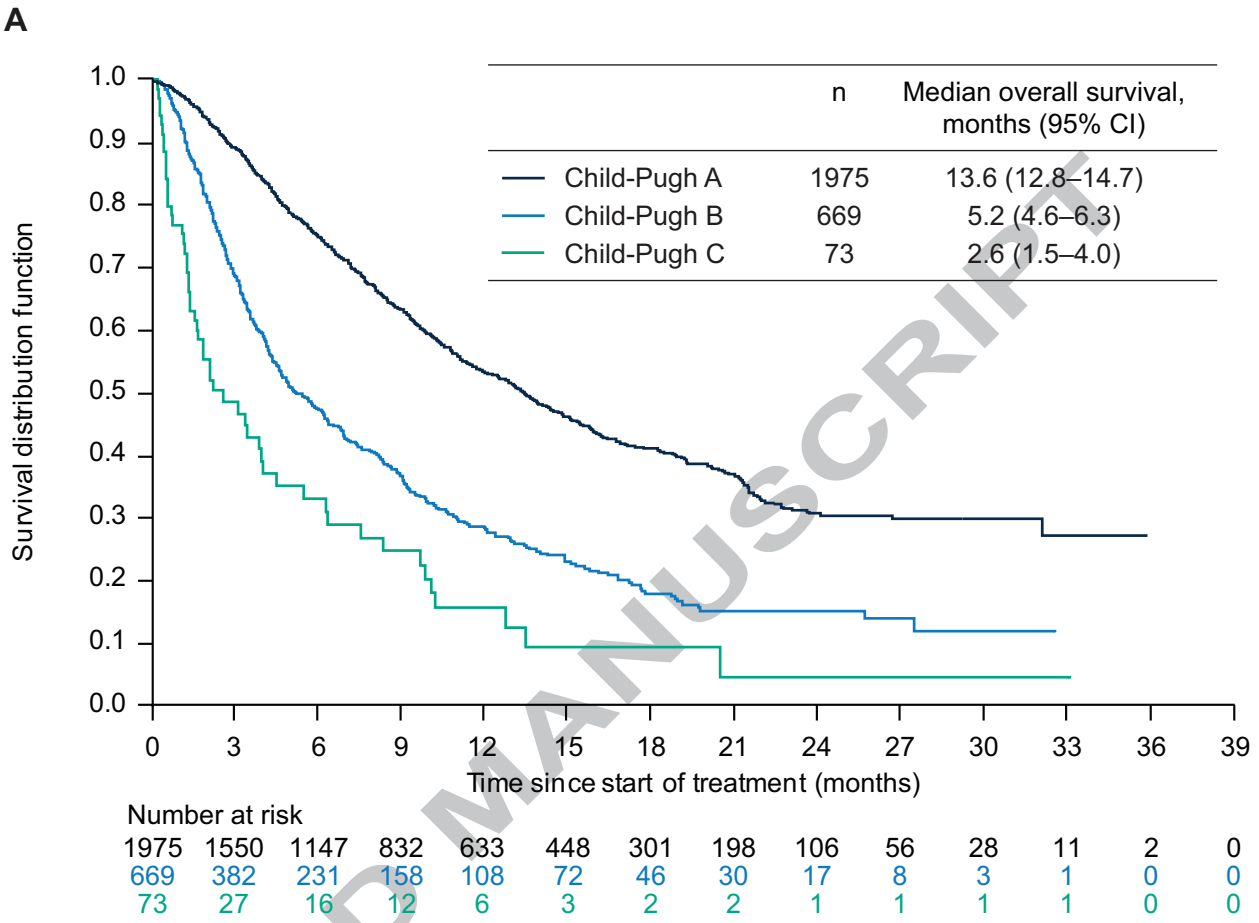
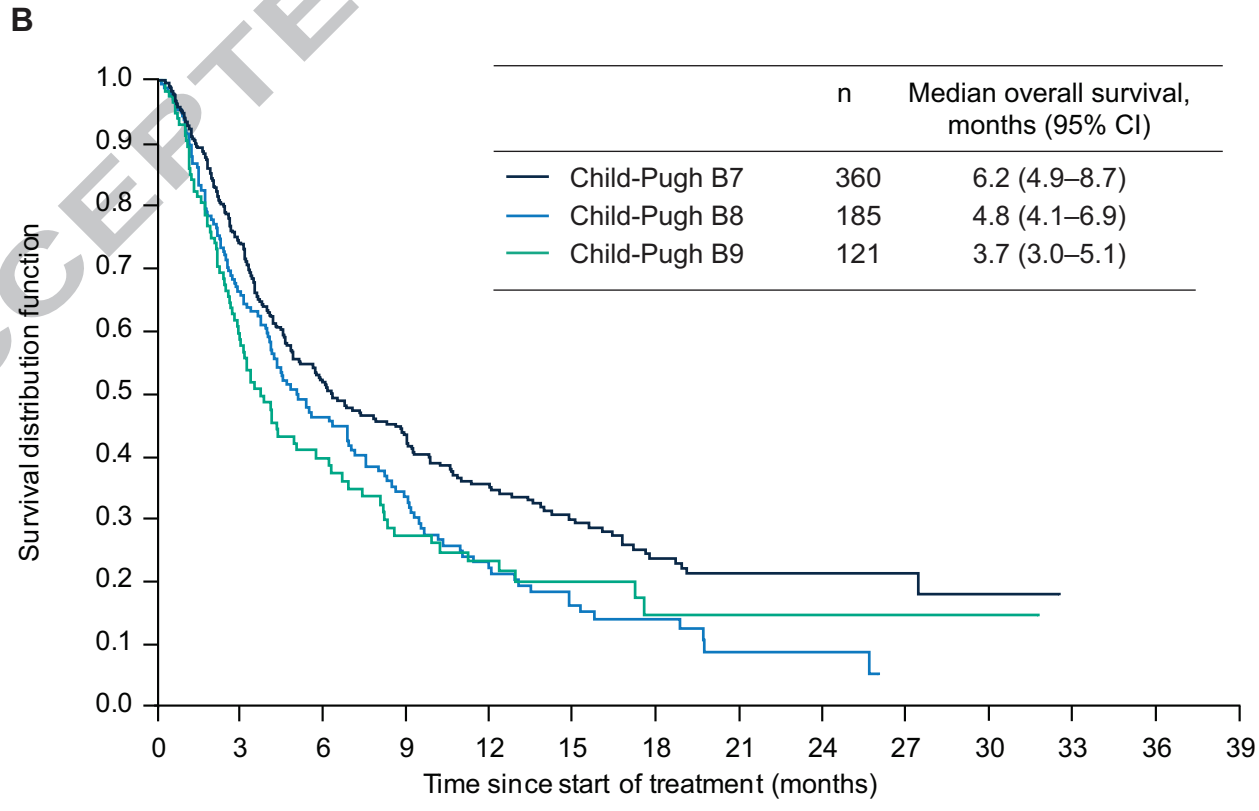


Figure 2







Graphical abstract